Acrylonitrile

Toxicological overview

Key Points

Kinetics and metabolism

- Acrylonitrile is readily absorbed into the systemic circulation, following ingestion, inhalation or dermal exposure
- Acrylonitrile can undergo metabolism either by glutathione conjugation which yields 2-cyanoethylmercapturic acid or cytochrome P450 oxidation which yields 2-cyanoethylene oxide, which can be further metabolised into cyanide
- Acrylonitrile does not accumulate in the body, the majority of an absorbed dose is excreted as metabolites in the urine 24-48 hours after exposure

Health effects of acute exposure

- Acute inhalation of acrylonitrile can cause symptoms including nose and throat irritation, nausea, dizziness, vomiting, ataxia and fatigue
- A more severe exposure may cause tremors, collapse, convulsions, mild jaundice, low grade anaemia and could possibly be fatal
- Ingestion of acrylonitrile is not a common route of exposure, but similar health effects would be seen to those resulting from inhalation
- Dermal exposure of acrylonitrile may result in severe localised irritation, with pain, blistering, erythema, itching, peeling and delayed healing
- Acrylonitrile may be absorbed into the systemic circulation following a dermal exposure, resulting in systemic toxicity similar to those observed following inhalation

Health effects of chronic exposure

- Chronic occupational exposure to acrylonitrile may cause adverse health effects including headache, insomnia, chest pains, fatigue, general malaise and irritability
- Acrylonitrile is a skin sensitizer and repeated dermal exposure to low concentrations may result in allergic dermatitis
- Acrylonitrile is considered to be a possible human carcinogen

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Toxicological Overview

Summary of Health Effects

Acrylonitrile is an irritant and causes severe irritation to any tissues with which it may come into contact [1].

Acrylonitrile is readily absorbed and can result in toxicity from all routes of exposure. Exposure to acrylonitrile may result in systemic toxicity in addition to the local toxicity at the site of contact [1].

Acrylonitrile poses a serious occupational inhalation hazard as it readily forms a high vapour concentration at room temperature [2, 3]. An acute exposure to acrylonitrile by inhalation can result in symptoms such as irritation of the nose and throat, nausea, vomiting, dizziness, fatigue, ataxia, irritability and apprehension. A more severe exposure to acrylonitrile may give rise to tremors, convulsions, collapse, mild jaundice, low grade anaemia and if the exposure is sufficient, may be fatal [1-3].

Ingestion of acrylonitrile is not a common route of exposure. However, its ingestion may cause similar symptoms to that observed following the inhalation of acrylonitrile vapours. Additional symptoms that may be seen following acrylonitrile ingestion would include mouth, throat and gastrointestinal tract irritation, abdominal pain and vomiting [1, 2].

Dermal exposure to acrylonitrile causes severe irritation, with symptoms of pain, blistering, erythema, itching, peeling and delayed healing. Acrylonitrile may be absorbed through the skin giving rise to systemic effects as observed following inhalation or ingestion. In some susceptible individuals, dermal exposure to acrylonitrile can cause skin sensitisation leading to the onset of allergic dermatitis [1, 2]. Ocular exposure to acrylonitrile may also result in severe irritation of the eyes, with erythema and pain [2, 3].

Long term occupational exposure to acrylonitrile vapour can lead to adverse health effects on the central nervous system, including headache, insomnia, chest pains, fatigue, general malaise and irritability. Inhalation of acrylonitrile vapour has also been shown to reduce haemoglobin, erythrocyte and white blood cell counts in individuals exposed over a long term [1, 2].

There is no evidence to suggest that acrylonitrile causes any significant reproductive or developmental toxicity in either humans or experimental animals [2].

There is sufficient evidence to suggest that acrylonitrile is carcinogenic to laboratory animals and there is some evidence that it produces lung cancer in workers, but the International Agency for Research on Cancer (IARC) consider this to be inadequate and overall classify it as possibly carcinogenic to humans (Group 2B) [4]. Acrylonitrile is classified under the EU system as a category 2 carcinogen, meaning that it is a substance which should be regarded as if it were carcinogenic to humans.

Kinetics and metabolism

Acrylonitrile is readily absorbed into the systemic circulation following exposure by inhalation or ingestion. Following inhalation of acrylonitrile by humans, around 50% of an administered dose of acrylonitrile is absorbed [5]. Acrylonitrile also undergoes extensive dermal absorption following exposure to the skin, although at a much lower rate than following inhalation or ingestion [1].

Acrylonitrile can undergo metabolism in humans by two main pathways: glutathione conjugation and oxidation by cytochrome P450. The main product of glutathione conjugation of acrylonitrile is 2-cyanoethylmercapturic acid (N-acetyl-S-(2-cyanoethyl)cysteine) [1, 5]. Oxidation by cytochrome P450 2E1 forms 2-cyanoethylene oxide, which can also undergo glutathione conjugation to yield a series of metabolites which include cyanide and thiocyanate [5]. Studies in which wild-type mice were administered 40 mg kg^{-1} acrylonitrile were shown to form a maximum of 110 nmol of cyanide per gram in the liver (2.9 mg kg^{-1} cyanide) [6]. However, although it may play a role in the acute toxicity of acrylonitrile, the formation of cyanide is not considered to be solely responsible for the toxicity of acrylonitrile [7]. Acrylonitrile does not accumulate considerably in any organs, with the majority of the absorbed compound excreted as metabolites in the urine 24 to 48 hours after exposure [1, 5].

Sources and route of human exposure

The main source of exposure to acrylonitrile is occupational, since it is primarily used in industry, although individuals may be exposed to low concentrations of acrylonitrile from some consumer products and cigarette smoke [5]. In occupations where acrylonitrile is used, suitable personal protective equipment is recommended, to reduce the potential for exposure [3, 8].

The major routes of exposure to acrylonitrile are by inhalation of vapours and dermal absorption [1, 2, 5]. Acrylonitrile can also cause toxicity by ingestion. However, accidental ingestion in the workplace is unlikely [2]. As acrylonitrile is an irritant, accidental exposure to splashes of liquid or vapours may cause ocular irritation [2].

Acrylonitrile has also been detected in small amounts (much lower than occupational exposure) in the air and water surrounding industrial plants involved with its manufacture or use [1, 5]. Acrylonitrile has been detected in food which has been stored in containers manufactured from plastics constructed with acrylonitrile, such as ABS (acrylonitrile-butadiene-styrene), however, the amount of acrylonitrile which can be present in packaging for food has now been limited [9, 10].

Health Effects of Acute / Single Exposure

Human Data

General toxicity

Acrylonitrile is an irritant, causing severe irritation with any tissues which it may come into contact with. Acrylonitrile is toxic by all routes, is readily absorbed and causes systemic toxicity in addition to local toxicity [1].

One of the metabolites of acrylonitrile in the body is cyanide, and as such, the toxicity of acrylonitrile on the central nervous system shares some characteristics with those observed in cases of cyanide poisoning [5]. The formation of cyanide in the body is not however, solely responsible for the toxicity of acrylonitrile [7].

The UK workplace exposure limit for a long term (8 hour) exposure to acrylonitrile is 2 ppm (4.4 mg m^{-3}) [11].

Inhalation

Acrylonitrile readily forms a vapour at room temperature and is toxic by inhalation. As such, exposure to acrylonitrile poses a serious inhalation hazard [2, 3].

Some common symptoms of inhalation exposure to vapours of acrylonitrile include irritation of the nose and throat, headache, nausea, dizziness, fatigue, diarrhoea, vomiting, ataxia and feelings of fullness in the chest, nervous irritability and apprehension. More severe exposure to acrylonitrile by inhalation can lead to tremors, mild jaundice, convulsions, collapse, low grade anaemia and possibly death [1-3].

Ingestion

Ingestion of acrylonitrile is not a common route of exposure, with no reports of acrylonitrile ingestion in humans being available. However, it is expected that oral exposure would give rise to similar symptoms to those experienced following inhalation of acrylonitrile vapour. Acrylonitrile is an irritant and as such, additional symptoms of oral exposure to those from inhalation be expected to include irritation of the mouth, throat and gastrointestinal tract with abdominal pain and vomiting [1, 2].

Dermal / ocular exposure

Dermal exposure to acrylonitrile causes severe irritation at the point of contact, with erythema, blistering, itching, pain, peeling, and delayed healing. Acrylonitrile may be absorbed through the skin and sufficient dermal exposure will give rise to systemic effects as observed following inhalation of acrylonitrile vapour. Dermal exposure to acrylonitrile may lead to the onset of allergic dermatitis in some people [1, 2].

Ocular exposure to acrylonitrile liquid or vapours has also been observed to cause severe eye irritation with erythema and pain [2, 3].

Delayed effects following an acute exposure

In most cases, symptoms of acute acrylonitrile intoxication are resolved completely following removal from exposure, with no long term sequelae [2].

Animal and In-Vitro Data

General toxicity

Acrylonitrile is a respiratory, skin and eye irritant. Signs of acute acrylonitrile toxicity in laboratory animals include respiratory tract irritation and central nervous system disturbances which exhibit some similarity with the effects of cyanide. Neurotoxicity may develop following inhalation or ingestion. The neurotoxicity of acrylonitrile has two stages, the first of which develops within 1 hour of exposure and is characteristic of cholinergic overstimulation, the signs of which in rats are vasodilation, salivation, lacrimation, gastric secretion and diarrhoea [5, 12]. The second stage of neurotoxicity develops more slowly at around 4 or more hours after exposure with signs of CNS disturbances, such as tremor, ataxia, convulsions and respiratory failure [5, 12]. Some other symptoms of acute acrylonitrile toxicity in rats include respiratory irritation, superficial necrosis of the liver and haemorrhagic gastritis of the forestomach [5].

Inhalation

The 4-hour LC_{50} for acrylonitrile inhalation in laboratory animals ranged from 300 – 900 mg m^{-3} [5]. Rats, rabbits, dogs, cats and monkeys exposed to lethal concentrations of acrylonitrile showed an initial stimulation of respiration, followed by ataxia, apnoea, vomiting, convulsions, coma and death. Reddening of the skin and mucosa, lacrimation, nasal discharge and salivation was also observed [1].

Ingestion

The oral LD_{50} for acrylonitrile in common laboratory mammals ranges from 25 to 186 mg kg^{-1} body weight [1, 5]. The acute toxicity of acrylonitrile by ingestion exhibits the same effects as those seen with inhalation of acrylonitrile vapour. Acrylonitrile is irritating to the oesophagus and stomach. Rats given an acute oral dose of acrylonitrile displayed haemorrhagic necrosis of the forestomach [1]. Oral exposure of rats to acrylonitrile resulted in salivation, diarrhoea, lacrimation, vasodilation and CNS depression [7]. Adverse effects on the liver, adrenal glands and gastric mucosa have also been reported following acute oral exposure to acrylonitrile [5].

Dermal

The dermal LD_{50} for acrylonitrile in a number of common laboratory mammals ranged from 148 to 693 mg kg^{-1} body weight [5]. Skin irritation has been reported when acrylonitrile was applied to the shaved skin of rabbits, with local vasodilation and oedema observed after a 15 minute application. The effect was more severe as the duration of exposure increased, with necrosis occurring following a 20 hour dermal exposure [5].

Health Effects of Chronic / Repeated Exposure

Human Data

Inhalation

Long term occupational exposure to acrylonitrile by inhalation has been shown to give rise to adverse health effects on the central nervous system such as headache, insomnia, chest pains, general weakness, decreased working capacity, fatigue, general malaise and increased irritability [1, 2]. Occupational exposure to acrylontrile has also been shown to affect haematology, with reduced haemoglobin, erythrocyte and white cell counts in exposed individuals [1].

Dermal

Acrylonitrile is a skin sensitizer, and occupational dermal exposure can cause an allergic skin reaction in susceptible individuals. Following sensitisation, dermal exposure to even small amounts of acrylonitrile (0.1%) can cause outbreaks of dermatitis, with symptoms of erythema, oedema, rash and itching [2].

Genotoxicity

There is insufficient evidence to assess the genotoxicity of acrylonitrile in humans, as studies have shown differences in the incidence of chromosomal aberrations in occupationally exposed individuals [1, 2].

Carcinogenicity

There is some limited evidence to suggest that acrylonitrile induces lung cancer in occupationally exposed workers, but results were inconclusive. The International Agency for Research on Cancer (IARC) considered that there is inadequate evidence in humans for the carcinogenicity of acrylonitrile and classify it as possibly carcinogenic to humans (Group 2B) [4].

Reproductive and developmental toxicity

There is no information available regarding the reproductive and developmental toxicity of acrylonitrile in humans [2]

Animal and In-Vitro Data

Inhalation

A long term inhalation study in male and female Sprague Dawley rats exposed to 0, 20 and 80 ppm acrylonitrile for 6hr day^{-1}, 5 day $week^{-1}$ for 2 years, showed the presence of non-neoplastic histopathological changes in the central nervous system and inflammation of the nasal turbinates in the treated groups [2, 5]. The pathological changes in the brain at the highest concentration of acrylonitrile were most evident as focal gliosis and perivascular cuffing. Histopathological examination also identified the early onset of chronic renal disease in the groups treated with acrylonitrile at 20 ppm. The chronic renal disease was not visible in the groups treated with 80 ppm acrylonitrile, as there was a significant and consistent increase in mortality from days 211-240 to the end of the experiment for the male rats, and from days 361-390 to the end of the experiment for the females [5].

Ingestion

A long term oral study in Sprague Dawley rats exposed to 0, 35, 100 and 300 mg $litre^{-1}$ acrylonitrile in drinking water for 2 years gave rise to hyperplasia and hyperkeratosis of the squamous epithelium of the forestomach in both males and females [5]. An increased incidence of focal gliosis and perivascular cuffing was also noted following oral exposure to acrylonitrile, which was also observed following inhalation [5].

Genotoxicity

Acrylonitrile has been shown to give rise to reverse mutations in the Ames test for gene mutation in TA1535 and TA100 strains of *Salmonella typhimurium*, but only in the presence of hamster or rat S9 microsomal fraction [5]. Examination for clastogenicity using metaphase analysis and Chinese hamster ovary cells resulted in positive results both with and without metabolic activation [1, 5]. The mutagenicity of acrylonitrile has also been investigated by several studies using the mouse lymphoma L5178 TK+/- assay. Again, positive results were generally obtained with or without an exogenous source of metabolic activation [5]. These *in vitro* data clearly indicate that acrylonitrile has mutagenic potential.

Results from *in vivo* studies are less consistent and many have limitations precluding definite conclusions from being drawn [1, 5]. Results from assays for clastogenicity in bone marrow (metaphase analysis or micronucleus test) were inconclusive or negative, but in most cases there was no indication as to whether acrylonitrile reached the bone marrow. Positive results were obtained in a study of unscheduled DNA synthesis in the liver, but not in a separate study. Negative or equivocal results were obtained in UDS assays using other tissues. Positive results were obtained in a host mediated assay in which rats and mice were administered acrylonitrile i.p. and the urine tested for mutagenicity using the Ames test. DNA adducts have been reported in liver DNA following administration of acrylonitrile, however, inconsistent result were obtained in other tissues [5]. These data are sufficient to assume that acrylonitrile is an *in vivo* mutagen.

Carcinogenicity

The carcinogenicity of acrylonitrile has been fairly extensively investigated in the rat. An increase in tumours of the central nervous system, Zymbal gland, tongue, stomach, small intestine and mammary glands was observed in rats exposed to acrylonitrile either by

ingestion or inhalation [1]. The International Agency for Research on Cancer has concluded that there is sufficient evidence for the carcinogenicity of acrylonitrile in experimental animals [4].

Reproductive and developmental toxicity

There is insufficient evidence from experimental animal studies to conclude that acrylonitrile may cause reproductive or developmental toxicity. There is some evidence of fetotoxicity, teratogenicity and embryotoxicity in the offspring of rats exposed during pregnancy to acrylonitrile by inhalation or ingestion. However, these effects were only seen at doses that produced significant maternal toxicity [2, 5].

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